



# Potent Antimicrobial agents derived from Combination of Transition metal with Sulfa drugs

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## Abstract

In the present study a novel 4-oxo - 4-[[4-(N-(thiazol-2-yl)sulfamoyl) phenyl] amino] butanoic acid (OTSPAB) was prepared by reaction of succinic anhydride with Sulphathiazol. The prepared ligand was exemplified by physical and spectroscopic studies. The transition metal complexes viz.  $\text{Cu}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Mn}^{2+}$  and  $\text{Zn}^{2+}$  of OTSPAB were synthesized and characterized by different properties. All the prepared metal complexes and ligand were studied as antimicrobial agent. Among all the metal complexes,  $\text{Zn}^{2+}$  and  $\text{Cu}^{2+}$  metal complexes have shown significant activity.

**Keywords:** Succinic anhydride, Sulphathiazol, Magnetic moment, Spectroscopic study and Antifungal properties.

## Introduction

In inorganic chemistry most active research area is coordination chemistry. Recently, metals or their complexes show more attention<sup>1-5</sup> because they exhibit several antibacterial<sup>6-12</sup>, antitumor<sup>13-15</sup> and anticancer activities<sup>16,17</sup>. Various studies have indicated<sup>18-20</sup> that biologically active compounds become more bacteriostatic and carcinostatic by chelation. Such interaction of transition-metal ions with amino acids and peptides is of immense biological significance<sup>21-23</sup>. For the treatment of urinary, intestine and ophthalmic infections, scalds, ulcerative colitis they are also effectively applicable<sup>24</sup>. Nowadays, various sulfaonamides compounds are used as an anticancer agent<sup>25</sup>, antiviral HIV<sup>26</sup> and in Alzheimer's disease<sup>27</sup>. The compound based prepared from succinic anhydride derivatives with Sulphathiazol has not been noted for metal complexation so far. Therefore we prepared one compound which contains succinic anhydride and Sulphathiazol moieties, which may afford some good biologically active compound. In present research paper we discuss about synthesizes, characterization and biological studies of 4-oxo-4-[[4-(N-(thiazol-2-yl)sulfamoyl) phenyl] amino]butanoic acid (OTSPAB). Also its metal complexes based on literature serve regarding importance of complexes, it was thought to synthesis transition metal complexes of prepared ligand in order to improve in biological activity.

## Material and Methods

**Materials and measurements:** All the chemicals used were of laboratory grade received from Sigma-Aldrich. Sulphathiazol was taken direct purchase to Sigma-Aldrich. <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and DEPT-135 NMR spectra were recorded in CDCl<sub>3</sub> at room temperature using a Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution NMR Spectrometer, TMS was

applied as internal reference. Infrared spectra were recorded neat by ATR on a Thermo Nicolet iS50 FT-IR spectrometer and are reported in cm<sup>-1</sup>. HR-MS data were obtained in methanol, with Thermo Scientific Orbitrap Elite Mass spectrometer. Thermo Finigen Flash1101 EA (Italy) is used for elemental analysis and volumetrically method for metals<sup>28</sup>. Gouy Balance was used to measure Magnetic susceptibility of complexes were carried out by. At room temperature the electronic spectra of complexes were measured. Melting point is measured by open capillary method.

**Synthesis of 4-oxo-4-[[4-(N-(thiazol-2-yl)sulfamoyl) phenyl] amino]butanoic acid (OTSPAB):** The reaction mixture of succinic anhydride (0.01 mole) in ethanol and (0.01 mole) Sulphathiazol in ethanol was refluxed for 2-3 hrs. The finalised solid was washed with H<sub>2</sub>O and dried. Recrystallized from MeOH. Yield: 75.26 %, M.P. (185-191°C) was measurement with open capillary method and it is uncorrected. IR (cm<sup>-1</sup>): 2950-2850 (Ar C-C), 3450-3360 (CONH, NH<sub>2</sub>), 3430, 1680 (COOH), 1620-1680(C=C). <sup>1</sup>H-NMR (δ ppm, 500 MHz, CDCl<sub>3</sub>): 11.80 (s, 1H, -COOH), 8.32 (s, 1H, -N-H), 7.71-7.98 (m, 4H, Ar-H), 6.51-6.92 (d, 2H, CH=CH), 3.14 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C MNR (δ ppm, 125 MHz, CDCl<sub>3</sub>): 182.23, 172.62, 152.12, 148.07, 138.20, 129.38, 127.98. DEPT-135 (δ ppm, 125 MHz, CDCl<sub>3</sub>): 138.20, 129.38, 127.98.

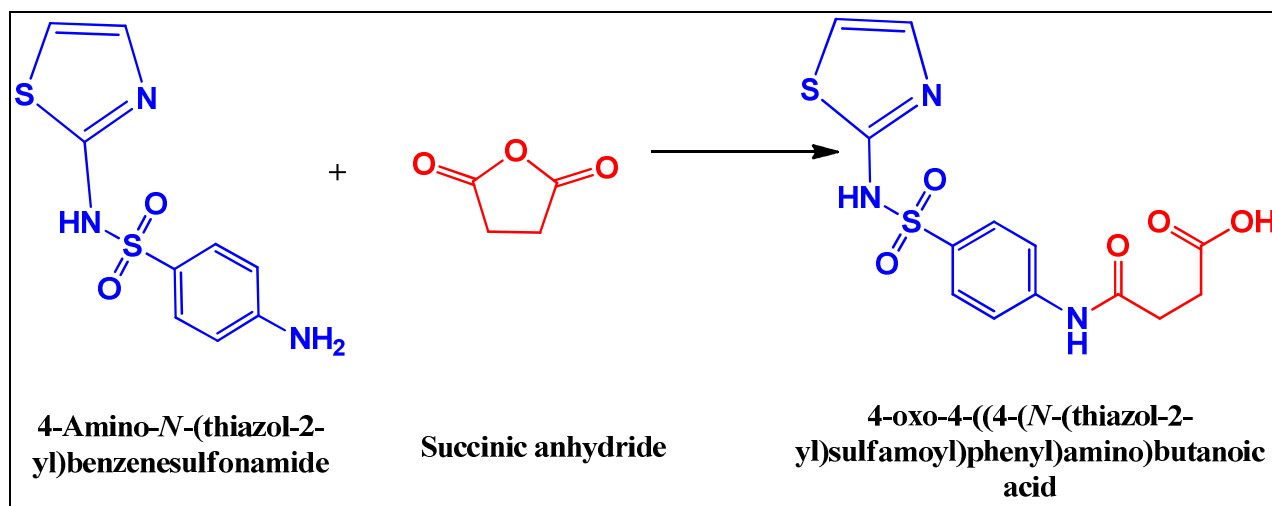
**Synthesis of metal complexes of 4-oxo-4-[[4-(N-(thiazol-2-yl)sulfamoyl) phenyl] amino]butanoic acid (OTSPAB):** The metal complexes of OTSPAB with  $\text{Cu}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Mn}^{2+}$  and  $\text{Ni}^{2+}$  transition metal were synthesized in following process. Same procedure is applied for other metal complexes.

**Preparation of OTSPAB solution:** The methanoic acid (85% v/v) was add up to slurry formed in OTSPAB (0.05 mol), until complete dissolution of OTSPAB and made to 20 ml.

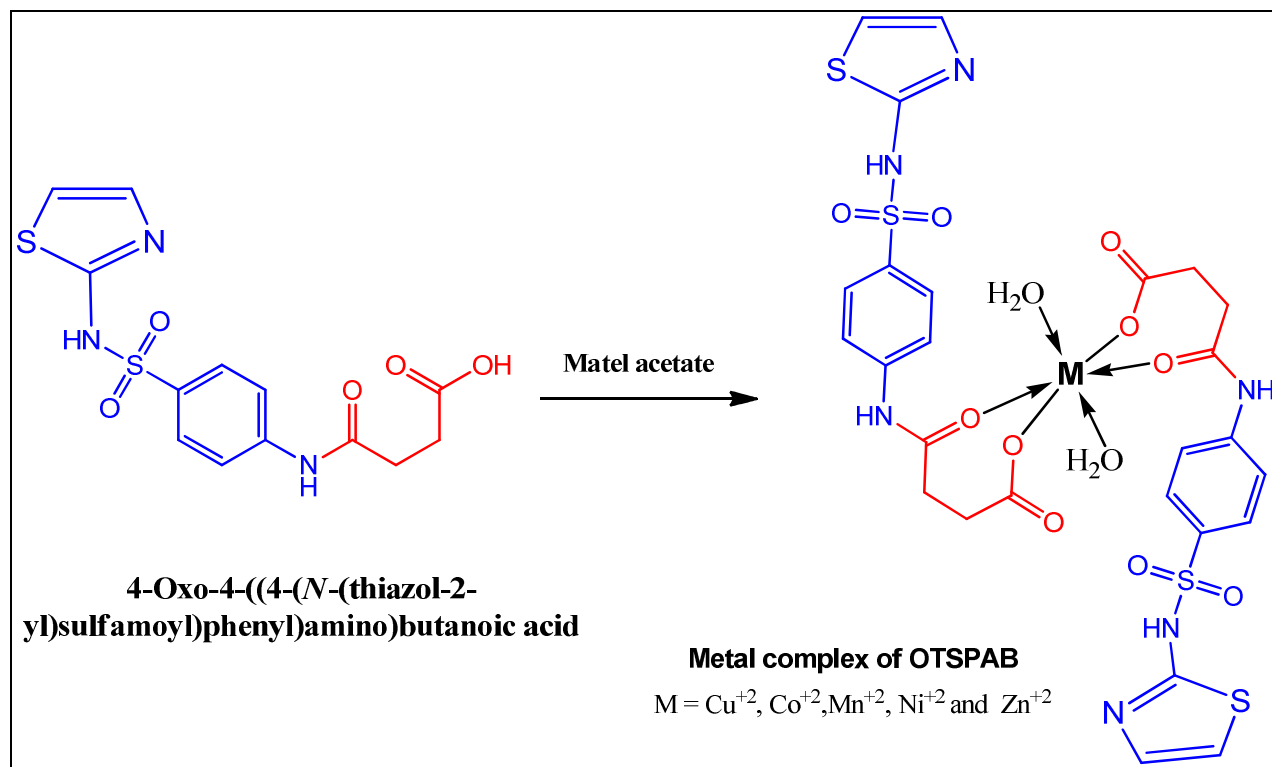
**Synthesis of OTSPAB -Metal-complexes:** The solution of metal acetate (0.025 mol) in  $\text{CH}_3\text{COCH}_3:\text{H}_2\text{O}$  (50:50 v/v) mixed (40 ml) with 20 ml of above OTSPAB solution (i.e. 0.05 M OTSPAB) was added. The suitable pH was regulated by adding NaOAc for absolute precipitation of metal chelate. The precipitates were digested and filter, washed and air-dried.

**Antibacterial activity:** The prepared ligand and its metal compounds were analysed for their antibacterial activities

against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* at a  $200 \mu\text{g ml}^{-1}$  concentration in DMSO by agar diffusion method using streptomycin as standard. The minimum inhibitory concentrations (MIC) were measured by serial dilution method. The stock solution ( $10^{-2}$  M) was prepared by dissolving the complex in DMSO and it diluted to different concentrations in the same solvent for the MIC values.



Scheme-1  
Synthesis of OTSPAB



Scheme-2  
Synthesis of metal complexes of OTSPAB

**Table-1**  
**OTSPAB and its metal complexes: Physical Analysis**

Empirical Formula	Yield (%)	Elemental Analysis									
		%Carbon		%Hydrogen		%Nitrogen		%Sulphur		%Metal	
		Theo.	Exp.	Theo.	Exp.	Theo.	Exp.	Theo.	Exp.	Theo.	Exp.
OTSPAB	76	43.93	43.90	3.69	3.60	11.82	11.75	18.04	17.90	-	-
(OTSPAB) <sub>2</sub> Cu <sup>2+</sup>	64	38.63	38.55	3.49	3.38	10.40	10.35	15.87	15.63	7.86	7.55
(OTSPAB) <sub>2</sub> Co <sup>2+</sup>	63	38.85	38.76	3.51	3.47	10.46	10.25	15.96	15.76	7.33	7.30
(OTSPAB) <sub>2</sub> Ni <sup>2+</sup>	65	38.87	38.77	3.51	3.44	10.46	10.33	15.96	15.88	7.30	7.28
(OTSPAB) <sub>2</sub> Mn <sup>2+</sup>	68	39.05	38.88	3.53	3.50	10.51	10.44	16.04	15.97	6.87	6.53
(OTSPAB) <sub>2</sub> Zn <sup>2+</sup>	64	38.54	38.50	3.48	3.35	10.37	10.31	15.83	15.77	8.07	8.00

Where: The = Theoretical. Exp = Experimental

## Results and Discussion

The synthesis of 4-oxo-4-[[4-(N-(thiazol-2-yl)sulfamoyl)phenyl] amino]butanoic acid (OTSPAB) was carried out by a simple reaction of succinic anhydride and Sulphathiazol. The synthesised OTSPAB was an amorphous brown powder. The C, H, N and metal contents of OTSPAB and its metal complexes (Table-1) are consistent with the predicted structure (Scheme-1). The Infrared spectrum of OTSPAB encompasses the significant bands of predicted structure.

The wide band at 3430 cm<sup>-1</sup> due to -OH group appeared. The <sup>1</sup>H NMR spectrum of OTSPAB point out that the singlet for 1H at 11.8 δ ppm due to -COOH group. The Ar-H are emerged in multiplicity at δ 7.7-7.9. Thus the structure of OTSPAB is confirmed as shown in Scheme-1.

The C, H, N and metal contents of metal complexes of OTSPAB (Table-1) are also consistent with the structure shown in scheme, which shows that 1:2 ratio for metal and ligand.

All the metal complexes are shows identical IR spectra and absence of band characteristic of free hydroxyl group of OTSPAB. All other bands are same as ligand. The important IR Spectral data are shown in Table-2.

The diffuse electronic spectrum of Cu<sup>2+</sup> complexes gives two wide bands in the region of 13190 and 23352 cm<sup>-1</sup>, which may be due to a <sup>2</sup>B<sub>1g</sub> → <sup>1</sup>A<sub>1g</sub> and charge transfer, respectively. It shows distorted octahedral structure for the Cu<sup>2+</sup> metal complexes. It also supported by the magnetic moment. Co<sup>2+</sup>

metal chelate gives 2 bands at 23825 and 19158 cm<sup>-1</sup>, which can be assigned <sup>4</sup>T<sub>1g</sub> → <sup>2</sup>T<sub>2g</sub>, <sup>4</sup>T<sub>1g</sub> → <sup>4</sup>T<sub>1g</sub>(P) transitions, respectively, which point out an Oh geometry of the metal chelate of Co<sup>2+</sup> [29]. The Mn<sup>2+</sup> chelate comprised 2 bands at 19162cm<sup>-1</sup> and 23321cm<sup>-1</sup> for <sup>6</sup>A<sub>1g</sub> → <sup>4</sup>T<sub>2g</sub>(G) and <sup>6</sup>A<sub>1g</sub> → <sup>4</sup>A<sub>2g</sub>(G) transitions, respectively. Some charge transfer characterized by high intensity of the bands. The experiential μ<sub>eff</sub> values in the range 2.52-5.60 B.M are reliable with the predicted structure<sup>29</sup>.

The antibacterial activity of OTSPAB and its metal complexes (Table-3) indicates that the OTSPAB is moderately toxic against bacteria, while other complexes are more toxic. Among them the Cu<sup>2+</sup> metal chelate is more toxic against tested bacteria.

## Conclusion

In the present study a novel 4-oxo - 4-[[4-(N-(thiazol-2-yl)sulfamoyl) phenyl] amino] butanoic acid (OTSPAB) was prepared by reaction of succinic anhydride with Sulphathiazol. The prepared ligand was exemplified by physical and spectroscopic studies. The transition metal complexes viz. Cu<sup>2+</sup>, Ni<sup>2+</sup>, Co<sup>2+</sup>, Mn<sup>2+</sup> and Zn<sup>2+</sup> of OTSPAB were synthesized and characterized by different properties. All the prepared metal complexes and ligand were studies as antimicrobial agent. Among all the metal complexes, Zn<sup>2+</sup> and Cu<sup>2+</sup> metal complexes have shown significant activity.

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**Table-2**  
**Magnetic moment and Spectral features of OTSPAB metal complexes**

Metal Complexes	$\mu_{\text{eff}}$ (BM)	Electronic spectral data ( $\text{cm}^{-1}$ )	Transition
OTSPAB-Cu <sup>2+</sup>	2.52	23352 13190	Charge transfer ${}^2B_{1g} \rightarrow {}^2A_{1g}$
OTSPAB-Ni <sup>2+</sup>	3.61	22576 15453	${}^3A_{1g} \rightarrow {}^3T_{1g}(P)$ ${}^3A_{1g} \rightarrow {}^3T_{1g}(F)$
OTSPAB-Co <sup>2+</sup>	4.72	23825 19158 8998	${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}$ ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$
OTSPAB-Mn <sup>2+</sup>	5.60	23321 19162 16993	${}^6A_{1g} \rightarrow {}^6A_{2g}$ ${}^4E_g$ ${}^6A_{1g} \rightarrow {}^4T_{2g}(4G)$ ${}^6A_{1g} \rightarrow {}^4T_{1g}(PG)$
OTSPAB-Zn <sup>2+</sup>	Diamag.	-----	-----

**Table-3**  
**OTSPAB and its metal complexes: antibacterial activity**

Compounds	Zone of inhibition at 1000 ppm (%)			
	<i>Escherichia coli</i>	<i>Klebsiella pneumonia</i>	<i>Proteus vulgaris</i>	<i>Staphylococcus aureus</i>
OTSPAB	54	56	51	60
OTSPAB-Cu <sup>2+</sup>	77	76	72	73
OTSPAB-Co <sup>2+</sup>	62	68	71	66
OTSPAB-Ni <sup>2+</sup>	58	67	63	64
OTSPAB-Mn <sup>2+</sup>	62	59	61	65
OTSPAB-Zn <sup>2+</sup>	76	72	61	75
Ampicillin	85	87	77	86

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